DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

1532 5 JUN 10 P2:13

Date: MAY 31 2005

From: Consumer Safety Officer, Division of Dietary Supplement Programs , Office of Nutritional Products, Labeling and Dietary Supplements, HFS-810

Subject: 75-Day Premarket Notification of New Dietary Ingredients

To: Dockets Management Branch, HFA-305

Subject of the Notification: _Lyophilised *Saccharomyes boulardii*_

Firm: ____Biocodex, Inc._____

Date Received by FDA: __February 8, 2005_____

90-Day Date: ___May 9, 2005_____

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification and related correspondence for the aforementioned substance should be placed on public display in docket number 95S-0316 as soon possible since it is past the 90-day date. Thank you for your assistance.

___*Victoria Lutwak*___

95S-0316

RPT 271

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
5100 Paint Branch Parkway
College Park, Maryland 20740

Mr. Nicolas Coudurier,
General Manager
Biocodex, Inc.
300 North Mill Street
P.O. Box 387
Creswell, OR 97426

MAY-23-2005

Dear Mr. Coudurier:

This is to inform you that the notification, dated January 28, 2005, you submitted pursuant to 21 U.S.C. 350b(a)(2)(section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act)) was filed by the Food and Drug Administration (FDA) on February 8, 2005. Your notification concerned the substance that you identified as "Lyophilised *Saccharomyces boulardii*" that you intend to market as a new dietary ingredient in a dietary supplement product that you call "Florastor®".

According to your notification, your new dietary ingredient will be marketed in capsules and sachets, each containing 250 mg of the ingredient, "Lyophilised *Saccharomyces boulardii*" and that consumers will be instructed to take one capsule or sachet in the morning and one in the evening.

Under 21 U.S.C. 350b(a), the manufacturer or distributor of a dietary supplement containing a new dietary ingredient that has not been present in the food supply as an article used for food in a form in which the food has not been chemically altered must submit to FDA, at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce, information that is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such new dietary ingredient will reasonably be expected to be safe. FDA reviews this information to determine whether it provides an adequate basis for such a conclusion. Under section 350b (a) (2), there must be a history of use or other evidence of safety establishing that the new dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. If this requirement is not met, the dietary supplement is considered to be adulterated under 21 U.S.C. 342(f) (1) (B) because there is inadequate information to provide reasonable assurance that the new dietary ingredient does not present a significant or unreasonable risk of illness or injury.

Two sections of your notification are labeled "Biocodex Ref. #9": one in English and one in French. There is no statement as to the accuracy of the translation of this or any of the other foreign language materials in the notification and there are two pages of English language material that does not correspond to anything in the French portion of "Biocodex Ref. #9". Because the translation of the foreign language material is not accompanied by an accurate and complete English Translation, the notification does not comply with the requirements of 21 CFR 190.6(b)(4)[1].

Nevertheless, FDA has carefully considered the information in your submission and the agency has concerns about the evidence on which you rely to support your conclusion that a dietary supplement containing "Lyophilised *Saccharomyces boulardii*" will reasonably be expected to be safe.

Your notification fails to clearly identify the new dietary ingredient because the notification did not include an adequate description of the final composition of your new dietary ingredient, "Lyophilised *Saccharomyces boulardii*". For example, it is not clear if your ingredient is composed solely of the organism or also includes culture medium or other substances introduced during production. In addition, while most of the safety information included in your notification contains explicit references to "*Saccharomyces boulardii*", it is not clear how the test materials used in clinical trials for the treatment of diarrhea are related to your product. For example, it is not clear whether the studies published over a 25 year period all employed organisms that are otherwise related to the "Lyophilised *Saccharomyces boulardii*" that is the subject of your notification. Furthermore, while you state on page 2 that each capsule or sachet of your product will contain "250 mg (5 billion live freeze dried cells)" ($2x10^{10}$ cells/1000 mg), material in reference 9 suggests that the contents of a sachet can vary from 4×10^8 to 4×10^{10} "freeze-dried live cells of *Saccharomyces boulardii*" per 200 mg. Most of the other references in your notification describe the administered dose in clinical trials in units of mass but not viable organisms. Therefore, it is not clear how the substances which were administered in clinical trials for treatment or prevention of diarrhea are qualitatively and quantitatively similar to "Lyophilised *Saccharomyces boulardii*" or how these trials are relevant to evaluating the safe use of your new dietary ingredient under the recommended conditions of use in a dietary supplement product.

Furthermore, you state on page 2 of your notification that "*S. boulardii* has been used extensively and safely in over 50 countries to relieve and prevent the symptoms of diarrhea... as either a dietary supplement or an over the counter (OTC) drug." The composition and conditions of use of the listed products are not described in the notification and thus it is unclear to FDA how these products are qualitatively and quantitatively similar to the dietary supplement product that you intend to market in the United States or how the history of use of

---

[1] Your notification also fails to correctly identify the botanical which is the subject of the notification. The notification erroneously uses the name "*Saccharomyces boulardii*" to describe what appears to be *Saccharomyces cerevisiae* Meyen ex E.C. Hansen var. *cerevisiae* (*S. cerevisiae*). Under the requirements of 21 CFR 190.6(b)(2) and of 21 CFR 101.4 (h) the Latin binomial name must be stated in accordance with the internationally accepted rules on botanical nomenclature.

these products is relevant to a determination that the product that you intend to market as a dietary supplement as defined in the United States by the Act can reasonably be expected to be safe under the conditions of use described in your notification.

For the reasons discussed above, the information in your submission does not provide an adequate basis to conclude that "Lyophilised *Saccharomyces boulardii*" when used under the conditions recommended or suggested in the labeling of your product, will reasonably be expected to be safe. Therefore, your product may be adulterated under 21 U.S.C. 342(f)(1)(B) as a dietary supplement that contains a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury. Introduction of such a product into interstate commerce is prohibited under 21 U.S.C. 331(a) and (v).

Your notification will be kept confidential for 90 days after the filing date of February 8, 2005. After the 90-day date, the notification will be placed on public display at FDA's Docket Management Branch in docket number 95S-0316. Prior to that date, you may wish to identify in writing specifically what information you believe is proprietary, trade secret or otherwise confidential for FDA's consideration.

If you have any questions concerning this matter, please contact Linda S. Pellicore, Ph.D. at (301) 436-2375.

Sincerely yours,

Susan J. Walker, M.D.
Director
Division of Dietary Supplement Programs
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety and Applied Nutrition

New Dietary Ingredient Notification
For
Saccharomyces Boulardii

Submitted By

Biocodex, Inc.
300 North Mill Street
P.O. Box 387
Creswell, Oregon 97426

January 28, 2005

Submitted To

Susan WALKER, M.D.,
Division of Dietary Supplements Programs (HFS – 810)
Office of Nutritional Products, Labeling and Dietary Supplements
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, Maryland 20740

From: **Biocodex, Inc.**
300 North Mill Street
P.O. Box 387
Creswell, Oregon 97426

To: Susan WALKER, M.D.,
Division of Dietary Supplements Programs (HFS – 810)
Office of Nutritional Products, Labeling and Dietary Supplements
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, Maryland 20740

Re: New Dietary Ingredient Notification

Date: January 28, 2005

Dear Dr. Walker:

Biocodex, Inc. is hereby submitting a New Dietary Ingredient (NDI) notification under 21 CFR § 190.6 for Lyophilised *Saccharomyces Boulardii* ("*S. boulardii*"), the dietary ingredient in our dietary supplement, Florastor®.

By way of background, this is the second NDI notification that we have submitted to the FDA. We submitted an NDI notification on March 16, 2004. On March 18, 2004, Vickey Lutwak from your office informed us by email that our notification had not been prepared according to the requirements in 21 CFR § 190.6. Specifically, we had failed to provide English translations of scientific publications containing evidence of the safety of using *S. boulardii* as recommended in Florastor® dietary supplements.

In this NDI notification for *S. boulardii* we provide all of the information required under 21 CFR § 190.6. We appreciate the helpful information provided by your office to assist us in preparing this notification.

1. Name and address of distributor and/or manufacturer

Distributor:

Biocodex, Inc.
300 North Mill Street
P.O. Box 387
Creswell, Oregon 97426

Manufacturer:

Biocodex
1 Avenue Blaise Pascal
60000 Beauvais, France

2. Name of new dietary ingredient

Lyophilised *Saccharomyces boulardii*

3. Description of the dietary supplement that contains the new dietary ingredient

Description of dietary ingredient

S. boulardii is non-pathogenic yeast in the dietary supplement, Florastor®. *S. boulardii* is a probiotic that has been used widely in over 50 countries to prevent and relieve the symptoms of diarrhea. *S. boulardii* is not digested and absorbed in the gut and does not exert its effect systemically. Instead, *S. boulardii* acts locally in the lumen of the gut. During its passage through the intestine, *S. boulardii* mimics the physiological effects of the digestive flora.

Description of dietary supplement

Florastor® will be sold in the U.S. as a capsule (10 or 50 capsules/bottle) or a sachet (10 sachets/box), each containing live, freeze-dried lyophilized *S. boulardii* cells in powdered form.

Level of new dietary ingredient in the dietary supplement

Each capsule or sachet of Florastor® contains 250 mg (5 billion live freeze dried lyophilized cells) of *S. boulardii*.

Recommended conditions of use

The package labeling instructs consumers to take one capsule or sachet in the morning and one in the evening for a total of 2 units/day (500 mg/day).

4. Evidence that the new dietary ingredient can reasonably be expected to be safe when used as recommended

History of use

S. boulardii has been used extensively and safely in over 50 countries to relieve and prevent the symptoms of diarrhea. Biocodex Laboratories has manufactured and sold products containing *S. boulardii* (Ultra-levure™, Floratil™, Perenterol™) for over 40 years. *S. Boulardii* containing products have been approved for sale by over 50 countries worldwide, including 11 members of the European Union, as either a dietary supplement or an over the counter (OTC) drug.

S. boulardii has a well-established record of safe use by people of all ages (infants, children and adults), ethnicities and cultures. No serious side effects have been attributed to the use of *S. Boulardii* when used as recommended.

Scientific Publications

In addition to an extensive history of safe use worldwide, *S. boulardii* has been extensively clinically tested in rigorous scientific studies, many of which were randomized, double blind, placebo controlled studies.

We have enclosed copies of twelve (12) scientific studies in which *S. boulardii*, manufactured by Biocodex, was tested as a therapeutic agent to treat or prevent various forms of diarrhea, including antibiotic-associated diarrhea, clostridium difficile-associated diarrhea, acute diarrhea, diarrhea associated with tube feeding, AIDS related diarrhea and travelers' diarrhea. Complete and accurate English translations of articles that were originally published in a foreign language have been provided. The complete citations of these twelve scientific publications and three revieew articles are provided in the bibliography attached as **Appendix I**.

The key results regarding safety and efficacy that were reported in these 12 scientific publications are provided in Table 1, attached as **Appendix II**. The numbers of the references in Table 1 correspond to the numbers in the bibliography in Appendix I. The references are grouped according to the patient population targeted in the study.

The maximum daily dose of *S. boulardii* used in eight (8) of the studies exceeded the recommended daily dose for Florastor® (500 mg/day) and ranged as high as 3000 mg/day (Ref. #11). The last column (far right) presents conclusory comments made in the articles regarding the safety of *S. boulardii*. None of the references reported any serious side effects. In fact, several articles reported that the tolerability of *S. boulardii* was excellent.

Summary

Both an extensive history of commercial use and rigorous scientific tests have shown that *S. boulardii*is safe when used at the recommended dose in Florastor® (500 mg/day) or even much higher doses (tested up to 3000 mg/day).

Please do not hesitate to contact me if you have any questions about the information provided in this NDI notification or if you need any additional information.

Best regards,

Nicolas Coudurier
General Manager
Biocodex, Inc.
ncoudurier@biocodexusa.com

Appendix I
Saccharomyces Boulardii Bibliography

Scientific Publications

1. McFarland LV, Surawicz CM, Greenberg RN, Elmer GW, Moyer KA, Melcher SA, Bowen KE, and Cox JL. Prevention of β-lactam associated diarrhea by *Saccharomyces boulardii* compared with placebo. The American Journal of Gastroenterology, 90 (3): 439-448 (1995).

2. Surawicz CM, Elmer GW, Speelman P, McFarland LV, Chinn J, and Van Belle G. Prevention of antibiotic-associated diarrhea by *Saccharomyces boulardii*: A prospective study. Gastroenterology, 96 (4): 981-988 (1989).

3. Adam J, Barret A, Barret-Bellet C, *et. al.* Controlled double blind clinical trials of Ultra-levure: Multi-center study involving 25 physicians and 388 cases. Médecine et chirurgie digestives, 5 (6): 401-406 (1976).

4. McFarland LV, Surawicz CM, Greenberg RN, Fekety R, Elmer GW, Noyer KA, Melcher SA, Bowen KE, Cox JL, Noorani Z, Harrington G, Rubin M, and Greenwald D. A randomized placebo-controlled trial of *Saccharomyces boulardii* in combination with standard antibiotics for Clostridium difficile disease. JAMA, 271: (24) 1913-1918 (1994).

5. Buts JP, Corthier G, and Delmee M. *Saccharomyces boulardii* for *Clostridium difficile*-associated enteropathies in infants. Journal of Pediatric Gastroenterology and Nutrition, 16: 419-425 (1993).

6. Hecker H. Results of a multicentre postmarketing surveillance study: Perenterol treatment in small children with diarrhea. Kinder- und Jungendmedizin, 2: 48 – 49 (2000).

7. Hoechter W, Chase D, and Hagenhoff G. *Saccharomyces boulardii*in acute adult diarrhea. Münchener Medizinische Wochenschrift, 132 (12): 188-192 (1990).

8. Chapoy P. Treatment of infantile acute diarrhea: Controlled trial of *Saccharomyces boulardii*. Annales de Pédiatrie, 32 (6): 561-563 (1985).

9. Cetina-Sauri G, Sierra Basto G. Therapeutic evaluation of *Saccharomyces boulardi* in children with acute diarrhea. Annales de pédiatrie, 41 (6): 397-400 (1994). English translation of original article: Trib. Med. (56(2): 111-115 (1989).

10. Bleichner G, Blehaut H, Mentec H, and Moyse D. *Saccharomyces boulardii* prevents diarrhea in critically ill tube-fed patients. Intensive Care Medicine, 23: 517-523 (1997).

11. Saint-Marc T, Blehaut H, Musial C, and Touraine JL. AIDs-related diarrhea: A double blind trial of *Saccharomyces boulardii.* Semaine des Hôpitaux, 71 (23-24): 735-741 (1995).

12. Kollaritsch R, Holst R, Grobara P, and Wiedermann G. Prophylaxis of traveler's diarrhea with *Saccharomyces boulardii*. Fortschritte der Medizin, 111 (9): 152-156 (1993).

Review Articles

13. Davidson GP and Butler RN. Probiotics in pediatric gastrointestinal disorders. Current Opinion in Pediatrics, 12 (5): 477-481 (2000).

14. Elmer GW. Probiotics: "Living drugs." Am. J. Health-Syst. Pharm., 58 (12): 1101-1109 (2001).

15. McFarland LV and Bernasconi P. *Saccharomyces boulardii*: A review of an innovative biotherapeutic agent. Microbial Ecology in Health and Disease, 6: 157-171 (1993).

Appendix II

Table 1. Summary of scientific publications included in this Notification of a New Dietary Ingredient reporting safety and effectiveness of *Saccharomyces. Boulardii* (S.B.) in clinical trials. (Reference numbers correspond to bibliography in Appendix I.)

Ref #	Study	Age of Subjects (yrs)	# of Subjects	Daily Dose (mg/day)	Efficacy	Safety
	Antibiotic-associated diarrhea					
1	McFarland, et al. *The Am. J. Gastroenterol.* (1995)	18 -86	193	1000	S.B. was effective in decreasing incidence of diarrhea: S.B. group: 7/97 (7.2%) Placebo: 14/96 (14.96%)	No significant adverse events were reported among patients receiving S.B.
2	Surawicz, et al. *Gastroenterol* (1989)	18 – 100	180	250	S.B. was effective in decreasing incidence of diarrhea: S.B. group: 11/116 (9.5%) Placebo: 14/64 (21.8%)	No side effects were reported.
3	Adam, et al. *Médecine et Chirurgie Digestives* (1976)	≤ 16	388	250	S.B. was effective in decreasing incidence of diarrhea: S.B. group: 9/199 (4.52%) Placebo: 33/189 (17.5%)	No side effects were reported.
	Clostridium difficile-associated diarrhea (CDD)					
4	McFarland, et al. *JAMA* (1994)	Adults	124	1000	S.B. was effective in decreasing incidence of recurrence of CDD: S.B. group: 26.3% recurrence Placebo: 44.8% recurrence	Thirst (n = 5) Constipation (n = 8)
5	Buts, et al. *J. Ped. Gastroenterol.* (1993)	0.2 - 11	19	< 1yr: 500 1-4yr: 750 >4yr: 1000	S.B. eliminated diarrhea in 18/19 (95%) subjects.	No side effects were reported.

Ref #	Study	Age of Subjects (yrs)	# of Subjects	Daily Dose (mg/day)	Efficacy	Safety
	Acute diarrhea					
6	Hecker, *Kinder- und Jugendmedizin* (2001)	0 – 17	940	50-1500	Physicians' assessment of S.B. (Perenterol) in children: Efficacy: "very good" = 52%; "good" = 38% Tolerability: "very good" = 70%; "good" = 29%	1.7% experienced side effects (flatulence or allergic reactions). "The safety of using Perenterol [*S. boulardii*] even in small children, which had already been empirically shown during many years of extensive use …, was confirmed during the present study ***."
7	Hoechter, et al., *Munch. Med. Wschr.* (1990)	18-65	92	150 – 200	S.B. significantly decreased frequency of loose stools within 2 days: S.B. group: 17.2% reduction Placebo: 13.6% reduction	"No severe side effects were observed in any patient." One patient in each group (S.B. and placeo) reported constipation or vomiting.
8	Chapoy, et al. *Annal. de Ped.* (1985)	Infants	38	500	S.B. significantly decreased the frequency and weight of loose stools.	"No side effects were noted and the acceptability of treatment was excellent."
9	Cetina-Sauri and S. Basto, *Trib. Med.* (1989)	0.25 - 3	130	800	S.B. significantly decreased the number of loose stools within 1 – 4 days.	"The number of clinical cures was larger than in the placebo group … there were no side effects."
	Tube-fed patients					
10	Bleichner, et al., *Int. Care Med.* (1997) Multi-center, randomized, double blind, placebo controlled study.	≤ 18	128	2000	S.B. significantly reduced the percentage of days with diarrhea: S.B. group: 14.2% Placebo: 18.9%	"The tolerance of *S. boulardii* was good and no adverse effect was noted."

Ref #	Study	Age of Subjects (yrs)	# of Subjects	Daily Dose (mg/day)	Efficacy	Safety
	AIDS					
11	Saint-Marc, et al. *Semaine des Hôpitaux* (1995) Randomized, double blind, placebo controlled study.	≥ 18	36	1500-3000	A significantly higher percentage of subjects receiving S.B had diarrhea resolved within 1 week: S.B. group: 61% resolved Placebo: 12% resolved	"Tolerability was outstanding." "[T]olerability of *S. boulardii* was excellent in all patients, with a total absence of adverse effects ...." "No clinical or paraclinical adverse events have occurred in the patients followed for a longer time."
	Traveler's Diarrhea					
12	Kollaritsch, et al., *Fortschr. Med.* (1993) Randomized, double blind, placebo controlled study.	> 6	1016	250-1000	S.B. reduced the rate of diarrhea: S.B. group (n = 655): 28.7% Placebo (n = 361): 39.1%	"No severe side effects or disorders necessitating discontinuation of administration were reported. This may demonstrate that the safety profile of SB is excellent and thus represents a more or less ideal prophylactic agent."

Biocodex, Inc.

New Dietary Ingredient Notification
Saccharomyces Boulardii

Publications